View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Yonsei University Medical Library Open Access Repository

J Korean Surg Soc 2012;82:335-339
http://dx.doi.org/10.4174/jkss.2012.82.6.335

JKSS
Journal of the Korean Surgical Society

pISSN 2233-7903 · eISSN 2093-0488

ORIGINAL ARTICLE

Impact of pretransplant rituximab induction on highly sensitized kidney recipients: comparison with non-rituximab group

Young Hae Song[1], Kyu Ha Huh[1,2], Yu Seun Kim[1,2], Hyung Soon Lee[1], Myoung Soo Kim[1,2], Soo Jin Kim[3], Hyun Jung Kim[2], Soon Il Kim[1,2], Dong Jin Joo[1,2]

[1]Department of Surgery, [2]The Research Institute for Transplantation, Yonsei University Health System, Seoul, [3]Department of Surgery, Bundang CHA Hospital, CHA University College of Medicine, Seongnam, Korea

Purpose: Highly sensitized patients with a high level of panel reactive antibody (PRA) experience more episodes of antibody-mediated rejection (AMR) and poorer graft survival than non-sensitized patients. Rituximab is a well-known monoclonal anti-CD20 antibody that causes the depletion of B lymphocytes. The aim of this study was to compare a rituximab-administered and a non-administered group of highly sensitized recipients. **Methods:** Forty-three kidney recipients with a PRA level of ≥50% were included. Sixteen (group R) received one dose of rituximab at 2 days prior to transplantation and 27 patients (group NR) did not. **Results:** Patients' demographics, such as age, sex, dialysis duration, and type of immunosuppressive agent were not different in the two groups. No side effects due to rituximab administration were observed in group R. Class I PRA of group R (75.6 ± 37.7%) was higher than that of group NR (45.7 ± 35.8%, P = 0.013). More acute rejection episodes occurred within 1 year after transplantation in group NR but the difference between the groups was not significant (18.8% in group R vs. 29.6% in group NR, P = 0.631). However, two AMR episodes occurred only in group NR. Renal functions were not different in the two groups. In group R, CD19 and CD20 rapidly decreased 2 days after rituximab infusion. Furthermore, the administration of rituximab was not linked to acute rejection. **Conclusion:** To confirm the long-term anti-rejection and beneficial effects of rituximab, further studies should be performed with a larger cohort. In conclusion, rituximab administration 2 days prior to transplantation is both effective and safe.

Key Words: Kidney transplantation, Immunological sensitization, Rituximab

INTRODUCTION

Patients who are exposed to foreign human leukocyte antigens (HLAs) during blood transfusion, pregnancy, or a previous transplant become sensitized [1,2]. Approximately 15% of male recipients are sensitized by transfusions before their first transplantation, and about 40% of women by pregnancies and transfusions [3]. Highly sensi-

Received January 9, 2012, Revised April 5, 2012, Accepted April 18, 2012

Correspondence to: Dong Jin Joo
Department of Surgery, Yonsei University Health System, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel: +82-2-2228-2105, Fax: +82-2-313-8289, E-mail: djjoo@yuhs.ac

This article was presented at 2011 The Korean Surgical Society Annual Autumn Congress.

Journal of the Korean Surgical Society is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2012, the Korean Surgical Society

tized patients show high levels of panel reactive antibody (PRA) in serum, have a greater risk of rejection episodes, and have poorer graft survival after kidney transplantation [4]. Rituximab has been widely used in desensitization protocols to prevent refractory antibody-mediated rejection (AMR) in these highly sensitized recipients [5-9]. In the present study, we focused on the impact of rituximab as an induction treatment for highly sensitized kidney recipients.

METHODS

Of the 627 kidney transplants performed in Yonsei University Health System between April 2006 and December 2010, we retrospectively reviewed the medical records of 43 patients with a high PRA (over 50%) in class I or II who underwent living donor renal transplantation. To avoid selection bias, deceased donor kidney transplant and pediatric recipients were excluded, as were ABO blood type incompatible kidney transplants, and negative conversion cases of recipients who showed pretransplant positive lymphocyte cross-matching (LCM) by plasmapheresis or by any other type of pretransplant desensitization protocol. Therefore, we used rituximab only for induction treatment.

PRA was screened by enzyme-linked immunosorbent assay method with Lambda Cell Tray lymphocytotoxicity assay (One Lambda Inc., Canoga Park, CA, USA) in all patients.

We divided the enrolled patients into two groups: group R (16 patients) were administered one dose (375 mg/m^2) of rituximab two days before transplant and group NR (27 patients) were not, because national medical insurance did not cover rituximab administration before June 2009, making this a historical control group. The two groups were compared retrospectively with respect to clinical characteristics, transplant outcomes, and CD19/CD20 change after transplantation. CD19/CD20 was measured immediately before rituximab administration, and 2 and 9 days after administration. LCM was performed before rituximab infusion at 2 days prior to transplantation. Rituximab infusion was started just after confirmation of a negative LCM result. Acute rejection was diagnosed clinically or by biopsy. Clinical rejection in this study was defined as a reduction in renal function with some signs of kidney swelling, an elevation of serum creatinine, and a reduction in urine output with no definite cause, treated by steroid pulse therapy without biopsy. Antibody mediated rejection was pathologically diagnosed by morphologic peritubular capillary staining for C4d, including capillary margination of inflammatory cells as described by Banff 97 [10].

Maintenance immunosuppression was performed using a calcineurin inhibitor-based regimen with or without antimetabolite. A low dose (5 mg or 10 mg/day) of prednisolone was maintained in all patients.

Continuous variables presented were analyzed using the two-tailed Student's t-test or the paired t-test, and results are presented as means ± standard deviations. Categorical variables were analyzed using the chi-square test and results are presented as proportions. P-values less than 0.05 were considered statistically significant.

RESULTS

Sixteen of the 43 highly sensitized patients received rituximab at 2 days before transplantation and 27 patients did not. Mean follow-up durations were 14.9 ± 4.6 and 38.1 ± 12.8 months for group R and group NR, respectively. Demographics, such as age, sex, dialysis duration and immunosuppressive agent type were no different for the two groups. No side effects, especially infectious complications of rituximab, were enrolled in group R. Mean class I PRA level of group R (75.6 ± 37.7%) was higher than in group NR (45.7 ± 35.8%, P = 0.013). However, class II PRA and HLA mismatches were not significantly different (Table 1).

More acute rejection episodes occurred in group NR during the first postoperative year but it did not reach statistical difference (18.8% in R vs. 29.6% in NR, P = 0.494) (Table 2). Three biopsy-proven acute rejections (18.8%) occurred in group R, and six biopsy proven acute rejections (22.2%) and two clinical rejections (7.4%) occurred in group NR. When biopsy proven acute rejections were clas-

Table 1. The pre-transplant clinical characteristics of groups R and NR

Characteristic	Group R (n = 16)	Group NR (n = 27)	P-value
Sex (male vs. female)	1 : 15	7 : 20	0.223
Age (yr)	46.1 ± 8.8	42.2 ± 10.5	0.214
Dialysis duration (mo)	18.5 ± 25.9	27.1 ± 30.7	0.388
PRA (%)			
Class I	75.6 ± 37.7	45.7 ± 35.8	0.013
Class II	37.6 ± 36.0	47.1 ± 36.3	0.410
HLA mismatching	2.9 ± 1.9	2.5 ± 1.3	0.416
Immunosuppressive agents			
Tacrolimus vs. cyclosporine	14 : 2	20 : 7	0.486

Values are presented as mean ± SD.
Group R, induction with rituximab administration; Group NR, no administration of rituximab; PRA, panel reactive antibody; HLA, human leukocyte antigen.

Table 2. The post-transplant clinical characteristics of groups R and NR

Characteristic	Group R (n = 16)	Group NR (n = 27)	P-value
Rejection episodes	3 (18.8)	8 (29.6)	0.494
Cell-mediated rejection	3 (18.8)	4 (14.8)	
Antibody-mediated rejection	0 (0)	2 (7.4)	0.631
Clinical rejection	0 (0)	2 (7.4)	
eGFR by MDRD (mL/min/1.73 m^2)			
1 Week after transplantation	55.0 ± 38.5	49.1 ± 27.4	0.557
1 Month after transplantation	53.2 ± 18.6	59.6 ± 14.9	0.227
3 Months after transplantation	52.9 ± 13.9	56.4 ± 7.6	0.403
6 Months after transplantation	51.0 ± 16.1	57.6 ± 11.6	0.152
9 Months after transplantation	52.7 ± 17.0	59.0 ± 10.5	0.165

Values are presented as number (%) or mean ± SD.
Group R, induction with rituximab administration; Group NR, no administration of rituximab; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

sified by rejection type, there was no AMR in group R and both AMR episodes occurred in group NR. One AMR was cured by steroid pulse therapy and the other by anti-thymocyte globulin after steroid pulse therapy.

The estimated glomerular filtration rate measured by modification of diet in renal disease was not different in the two groups at 1 week, and 1, 3, 6, and 9 months after transplantation (Table 2).

In group R, serum CD19 and CD20 were markedly decreased at 2 days after rituximab infusion (Fig. 1), and serum CD19 and CD20 at 2 and 9 days after rituximab infusion were significantly lower at 2 and 9 days after rituximab infusion than after pre-rituximab administration ($P < 0.0001$). However, at 9 days after rituximab infusion, only CD19 was lower than that at 2 days after rituximab administration ($P = 0.019$).

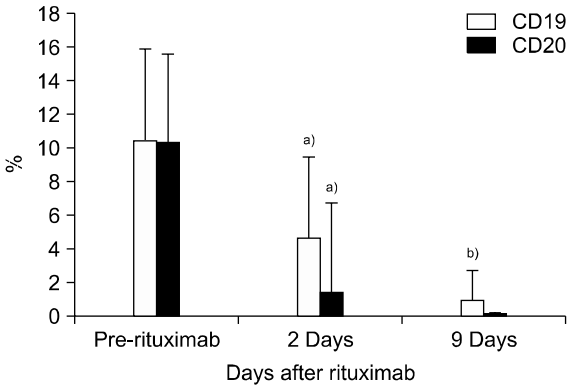

Fig. 1. Changes in serum CD19 and CD20 after rituximab infusion. [a]$P < 0.05$ compared with pre-rituximab status. [b]$P < 0.05$ compared with 2 days after rituximab.

DISCUSSION

Acute humoral rejection occurs in highly sensitized patients who develop *de novo* allospecific antibodies, or in those with pre-existing anti-HLA [11,12]. Rituximab has been used to eliminate anti-HLA and a degree of B-cell depletion is known to be correlated with serum rituximab levels [8]. Vieira et al. [13] reported that the use of rituximab decreased PRA from 87 to 51% with a concurrent decrease in fluorescence intensity. These reports suggest that rituximab provides benefits in terms of desensitization and reducing acute rejection episodes. In the current study, no significant differences in acute rejection episodes were observed between groups R and NR, though this could have been due to the small cohort size. Furthermore, the study is limited by the absence of follow-up PRA data and by the lack of a donor specific antibody (DSA) study at the time of AMR diagnosis. However, AMR only occurred in group NR. Further studies are required with a large cohort with follow-up PRA and DSA studies to confirm the beneficial effect of rituximab on AMR prevention.

Rituximab has been used for desensitization of ABO-incompatible organ transplants and in highly sensitized pa-

tients who were on a waiting list. The optimal AMR dosage is unknown and the amount administered for desensitization is based on the treatment of non-Hodgkin's lymphoma [7,14,15]. Many centers have used rituximab as an intravenous infusion of 375 mg/m^2 at 1 or 2 weeks before transplantation with plasmapheresis and intravenous immunoglobulin (IVIG) to deplete all peripheral B cells, as well as B cells, in renal tissue and lymph nodes [16-18]. However, to the best of our knowledge, few single pretransplant rituximab induction treatments have been conducted without plasmapheresis or IVIG in highly sensitized recipients. In the present study, we investigated the effect of single rituximab induction in highly sensitized kidney recipients. Only one dose of rituximab was administered 2 days before kidney transplantation in order to avoid a false positive LCM result due to B-cell depletion by rituximab. Rituximab was administered after confirming a negative LCM. The effect of rituximab on B cells in peripheral blood was rapid, and peripheral CD19+ cells were ablated within a few days [13,16]. Vieira et al. [13] also reported that the use of low-dose rituximab eliminated peripheral B cells within 2 days.

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody, and CD20 mediates B-cell proliferation and differentiation. CD20 antigen is not internalized upon antibody binding, and is not shed or found in soluble forms. Following treatment with rituximab, B cells are prevented from proliferating, and undergo apoptosis and lysis through complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and via the activations of tyrosine kinases as a direct effect of the antibody binding to its CD20 ligand [7,8,13]. To verify the effect of rituximab on B-cells, we checked CD19 and CD20, which are predominantly expressed on B cells. Because all CD20 positive B cells also express CD19, it serves as a surrogate marker for verifying the depletion of B cells by the blocking of CD20 epitope by rituximab [19]. It has also been suggested that rituximab can mask CD20 epitopes, and that this results in the false negative expression of CD20 of B cells in peripheral blood [18,20,21]. The results of the present study showed that CD19 and CD20 are markedly decreased within 2 days of rituximab administration.

Summarizing, this study shows the beneficial effects of rituximab administered at 2 days before transplantation. Considering the marked decrease in CD20 and CD19 and the lack in AMR increase after this administration, it appears that a single dose of rituximab administered in this manner is both a safe and feasible induction treatment in kidney recipients with a PRA of over 50%. However, further large-scale studies with follow-up PRA and DSA studies are required to confirm the prevention of AMR by rituximab.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the 2010-2011 research grant of the Research Institute for Transplantation, Yonsei University College of Medicine.

REFERENCES

1. Jordan S, Cunningham-Rundles C, McEwan R. Utility of intravenous immune globulin in kidney transplantation: efficacy, safety, and cost implications. Am J Transplant 2003;3:653-64.
2. Jordan SC, Pescovitz MD. Presensitization: the problem and its management. Clin J Am Soc Nephrol 2006;1:421-32.
3. Iwaki Y, Terasaki PI. Sensitization effect. Clin Transpl 1986:257-65.
4. Crespo M, Pascual M, Tolkoff-Rubin N, Mauiyyedi S, Collins AB, Fitzpatrick D, et al. Acute humoral rejection in renal allograft recipients: I. Incidence, serology and clinical characteristics. Transplantation 2001;71:652-8.
5. Alausa M, Almagro U, Siddiqi N, Zuiderweg R, Medipalli R, Hariharan S. Refractory acute kidney transplant rejection with CD20 graft infiltrates and successful therapy with rituximab. Clin Transplant 2005;19:137-40.
6. Aranda JM Jr, Scornik JC, Normann SJ, Lottenberg R, Schofield RS, Pauly DF, et al. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. Transplantation 2002;73:907-10.
7. Becker YT, Becker BN, Pirsch JD, Sollinger HW. Rituximab as treatment for refractory kidney transplant rejection. Am J Transplant 2004;4:996-1001.

8. Salama AD, Pusey CD. Drug insight: rituximab in renal disease and transplantation. Nat Clin Pract Nephrol 2006;2:221-30.
9. Sarwal M, Chua MS, Kambham N, Hsieh SC, Satterwhite T, Masek M, et al. Molecular heterogeneity in acute renal allograft rejection identified by DNA microarray profiling. N Engl J Med 2003;349:125-38.
10. Racusen LC, Colvin RB, Solez K, Mihatsch MJ, Halloran PF, Campbell PM, et al. Antibody-mediated rejection criteria: an addition to the Banff 97 classification of renal allograft rejection. Am J Transplant 2003;3:708-14.
11. Stegall MD, Gloor J, Winters JL, Moore SB, Degoey S. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. Am J Transplant 2006;6:346-51.
12. Munoz AS, Rioveros AA, Cabanayan-Casasola CB, Danguilan RA, Ona ET. Rituximab in highly sensitized kidney transplant recipients. Transplant Proc 2008;40:2218-21.
13. Vieira CA, Agarwal A, Book BK, Sidner RA, Bearden CM, Gebel HM, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. Transplantation 2004;77:542-8.
14. Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol 1997;15:3266-74.
15. Faguer S, Kamar N, Guilbeaud-Frugier C, Fort M, Modesto A, Mari A, et al. Rituximab therapy for acute humoral rejection after kidney transplantation. Transplantation 2007; 83:1277-80.
16. Genberg H, Hansson A, Wernerson A, Wennberg L, Tydén G. Pharmacodynamics of rituximab in kidney allotransplantation. Am J Transplant 2006;6:2418-28.
17. Yoon HE, Hyoung BJ, Hwang HS, Lee SY, Jeon YJ, Song JC, et al. Successful renal transplantation with desensitization in highly sensitized patients: a single center experience. J Korean Med Sci 2009;24 Suppl:S148-55.
18. Toki D, Ishida H, Horita S, Setoguchi K, Yamaguchi Y, Tanabe K. Impact of low-dose rituximab on splenic B cells in ABO-incompatible renal transplant recipients. Transpl Int 2009;22:447-54.
19. Tyden G, Genberg H, Tollemar J, Ekberg H, Persson NH, Tufveson G, et al. A randomized, doubleblind, placebo-controlled, study of single-dose rituximab as induction in renal transplantation. Transplantation 2009;87:1325-9.
20. Jilani I, O'Brien S, Manshuri T, Thomas DA, Thomazy VA, Imam M, et al. Transient down-modulation of CD20 by rituximab in patients with chronic lymphocytic leukemia. Blood 2003;102:3514-20.
21. Cragg MS, Bayne MC, Illidge TM, Valerius T, Johnson PW, Glennie MJ. Apparent modulation of CD20 by rituximab: an alternative explanation. Blood 2004;103:3989-90.